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COMPLEMENTARY AND ALTERNATIVE MEDICINES FOR INFECTIOUS DISEASES

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ABSTRACT

Complementary and alternative medicines (CAM) are widespread use**.** In U. S. adults 19% used herbal medicines. CAM is in use irrespective of prior demonstration of safety and efficacy. Both CAM and integrative medicine modalities are widely used by patients, including with infectious diseases. In a review of 40 studies of CAM and integrative medicine modalities have been used for common cold, recurrent urinary tract infections, (UTIs), malaria, diarrhea, and HIV/high active antiretroviral therapy (HAART) - associated hyper triglyceridemia.CAM also considered to be useful for HIV infected patients. Large placebo-controlled studies have shown that St. John's worts, garlic, milk thistle, gingko and chondroitin doesn't treat depression, lower low density lipoprotein, cholesterol, hepatitis, affect memory and arthritis respectively. Conversely, omega -3 fatty acids can prevent heart disease, calcium and vitamin D prevent osteoporosis in postmenopausal women and folic acid prevent neural tube defects in pregnancy. Individuals are often unaware that CAMs are not tested by the therapeutic Goods Administration for efficacy and safety.

KEYWORDS: CAM, Cranberries, Zinc and Milk Thistle

INTRODUCTION

Complementary or traditional medicines have been used for millennia .Personal effects found in melting alpine snows alongside the well-preserved ice man have included medicinal herbs. Despite the dramatic advances in health over past two centuries through conventional medicine, people have not abandoned their penchant for traditional medicinals. In a 2002, Centers for Disease Control and Prevention (CDC) survey of U. S. adults 19% used herbal medicines [1]. Complementary and alternative medicines (CAM) are widespread use, irrespective of prior demonstration of safety and efficacy. In contrast conventional agents first have to be shown to be safe and effective before being marketed and used. Alternative agents encompass botanicals and their extracts, extracts of animal tissues, vitamins, minerals, amino acids, and probiotics [2]. In the United States, as defined by the National Centre for complementary and Alternative Medicine (NCCAM), complementary and alternative medicine is a group of diverse medical and health care systems, practices, and products that are not presently considered part of conventional medicine and integrative medicine is medicine that combines treatments from conventional medicine and CAM for which there is some-quality evidence of safety and effectiveness [3]. Both CAM and integrative medicine modalities are widely used by patients, including with infectious diseases [4,5]. One review of 40 studies of CAM and integrative medicine modalities have been used include common cold, recurrent urinary tract infections (UTI), malaria, diarrhea, and HIV/highly active antiretroviral therapy (HAART) - associated hypertriglyceridemia [2]. In one study of 89 HIV care providers, 63% believed that CAM and integrative medicines therapies may be helpful for HIV infected patients and 36% had personally used one [6]. Excellent large, placebo-controlled studies have shown that St. John's wort doesn't treat depression, garlic doesn't lower low- density lipoprotein, cholesterol, milk thistle doesn't treathepatitis, gingko doesn't affect memory, and chondroitin sulfate and glucosamine don't treat arthritis. Because these therapies don't work they are not an alternative. Conversely,

omega-3 fatty acids can prevent heart disease, calcium and vitamin D in postmenopausal women can prevent osteoporosis, and folic acid during pregnancy can prevent neural tube defects. The same can be said for the value of eating lots of fruits and vegetables, getting plenty of exercise and sleep, and reducing stress [7]. This article reviews the use of CAM and integrative medicines by the patients.

ARTEMISININ FOR MALARIA

Malaria is caused by *Plasmodium falciparum* is an acute, often mortal disease characterized by cerebral dysfunction, respiratory failure, kidney dysfunction, and hypoglycemia in persons without immunity because of previous exposure. Once the patient has cerebral malaria, there is generally a 20 % death rate in spite of appropriate antimalarial therapy [8]. Ancient Chinese physicians identified an approach to fevers that held the secret to a new class of antimalarial drugs. In 340 AD the *Chinese Handbook of Prescriptions* for *Emergency Treatments* recommended drinking an aqueous extract of the leaves of *Artemisia annua* for fever [8]. Pursuing this early observation in 1971 and 1972, Chinese scientists found that ether was more successful than hot water in extracting material with anti-*Plasmodium* activity. Crystalline artemisinin is now available from the Chinese *Artemisininannua* and is the staring material for semisynthetic artemisinin now used worldwide. A. annua also grows along the Potomac River in Washington ,DC, but the yield from Potomac *A. annua* is 0.06% as liithe as one tenth the yield from the varieties grown in Szechuan province in China [8]. Artemisinins illustrates the general principal that local growth conditions of identical species may have a marked effect on the quality of botanical extracts.

Artemisinin asesquiterpine lactone peroxide, is poorly soluble in water [9]. Medicinal chemists have improved the solubility of artemisinin by the addition of a polar succinic acid group to form water –solubleartesunate or a nonpolar methyl group to form oil soluble artemether, both of which are essentially prodrugs and dihydroartemisinin. The active moiety of all the artemisinin is the end roperoxidering, which is thought to lead to alkylation and oxidation of essential proteins and lipids [9]. Completely synthetic peroxides are now being investigated. The peroxide group in artemisinin is unique with respect to known anti malarials and was entirely unanticipated by malarialologists [10].

Clinical artemisinin are effective against parasites resistant to all other antimalarial agents. The short half-lives of artemisinin have encouraged their co-administration with longer half-life agents, to fully clear the few parasites remaining after artemisinintreatment. The advent of artemisinin combinations as artemether-lumefantrineisartesunate-mefloquine into current formularies illustrates those traditional observations of efficacy of botanical extracts can be correct. In the case of *A. annua*, a discrete molecule was found to account for the extract's activity and that molecule was then developed according to conventional drug standards [2].

CRANBERRY FOR PREVENTION OF URINARY TRACT INFECTION

Native Americans were the first to use cranberries for their medical properties [11]. In 1880s, German physicians observed that urinary excretion of hippuric acid increased after ingestion of cranberries. In 1914, Blatherwick confirmed that cranberries are rich in benzoic acid, which is then excreted in the urine as hippuricacid [12]. Today, it is known that the low amount of benzoic acid present in the fruit (<0.1% of weight) coupled with maximum tolerated amounts of cranberries juice (4L/d), rarely results in enough hippuric acid excretion necessary to achieve bacteriostatic urinary concentration [13].

Approximately 80% of urinary tract infections (UTIs) are caused by *Escherichia coli* and from 25% to 35% of initial UTIs, including those caused by *E. coli*, recur within 6 months. *E. coli* possess surface organelles (fimbriae) that

bind to uroepithelial cell receptors. Type I fimbriae are expressed by almost all *E. coli* and contain a mannose-specific lectin. Most pyelonephritogenic strains of *E. coli* also express P fimbria, characterized by mannose- resistant adhesion molecules [14]. Cranberry juice, widely used for UTI, typically contains 3% glucose and 1% fructose; cranberry juice cocktail has added sugars and usually contains 7% glucose and 5% fructose [14]. Both pure 0.35% fructose and dilution of cranberry juice that resulted in 0.4% fructose inhibited adherence of type 1 fimbriated *E. coli* to mannose- sensitive receptors

UTI Prophylaxis: Pagas *et al*. described the effect of cranberry juice in 60 patients with bacteriuria who received 480ml of juice daily for three weeks. After therapy, 53% had positive response and additional 20% had modest benefit, but 6 weeks after stopping treatment, bacteriuria reappeared in most of the subjects [15].

UTI Treatment: The Cochrane reviewers concluded that randomized studies assessing effectiveness of cranberry juice for treatment of UTI have not yet been conducted. Therefore, at present, there is no evidence to suggest that cranberry juice or other cranberry products are effective for treatment of UTI [16].

ZINC FOR DIARRHEA IN CHILDREN IN THE DEVELOPING COUNTRIES

Zinc is divalent cation compared with iron and copper it is relatively stable to oxidation and reductions Zinc, therefore is an ideal metal cofactor for enzymatic reactions [17]. Hundreds of zinc metalloenzymes are known. The importance of zinc in infectious diseases is illustrated by acrodermatitisenteropathica, an auto so mal recessive disorder attributed to a defect in zinc metabolism. These patients suffer from diarrhea and immune dysfunction; including T-cell dysfunction susceptibility to viral, bacterial and fungal infections [18]. Unlike vitamin A. zinc does not have tissue reserve. Mild zinc deficiency can occur in breast fed children after six months of age if the diet does not include red meat which is the major dietary source of exogenous zinc [19].

In a meta- analysis of prophylaxis trials in which 5 to 20 mg zinc /day (the U.S. recommended daily allowance of zinc is 5 to 10 mg/day) was provided to children younger than 5 years in developing countries for 12 54 weeks, the pooled OR for diarrhea incidence (0.82) was statistically decreased with respect to controls [20]. Other large prophylaxis trials have been reported from south Africa and Bangladesh. In HIV- infected in South Africa, Zinc supplementation for 6 months (10mg, daily) halved the incidence of diarrhea and there was trend toward reduction of pneumonia [21]. The effect of zinc was direct, not indirect via a change in HIV status, because the HIV viral load was unaffected. In Bangladeshi, weekly supplementation with zinc (70mg) significantly decreased the risk of pneumonia, diarrhea, and death compared with placebo in 2-to 12 month-old infants. None of the zinc patients but 10 of the placebo patients died of pneumonia alone [22]. In South America, the number of episodes of diarrhea in Peruvian children aged 0.5 to 15 years was statistically diminished by the administration of zinc,20mg daily [23]. Zinc is also effective treatment for diarrhea in children in developing countries, although it may be necessary to enroll patients by day 3 or 4 of symptoms to achieve statistical evidence of benefit [24]. For Indian children 6 to 35 months of age, the relative risk of diarrhea lasting longer than 7 days was statistically reduced (RR=0.61) in zinc –supplemented children who enrolled by day 4 of symptoms, but in children who enrolled after any period of prior diarrheal symptoms (RR=0.87; range,0.65 to 1.16) [24]. Roy and co-workers [25]. have confirmed that if zinc supplementation (20mg/day) is started in Bangladeshi children 3 to 24 months old with diarrhea of less than 3 days' duration the time to recovery is shortened compared with controls (4.7 vs.6.2 days; $P<.04$).

In a more recent report, administration of three time the recommended daily allowance of zinc to Nepalese children with diarrhea of 96 hours or more significantly reduced disease duration. For patients whose diarrhea lasted longer

than 3 days after starting the study, the risk ratio for zinc patients compared with controls was 0.75 (range,0.61 to 0.91), and for the lesser number of cases lasting longer than 7 days, the risk ratio was 0.57 (range 0.38 to0.86). Plasma zinc values increased by approximately [26]. In Bangladeshi villages, zinc (20mg/dayx14 days) significantly lowered the duration of diarrhea in 3- to 59-month-old children by 1.2 day [27, 28]. Both prophylaxis and treatment have been studied in the younger age groups. Low- birth – weight Indian children were administered.5mg zinc or placebo daily from birth to 1 year age. The incidence of diarrhea was 1.4 episodes/child-year in the treated group, significantly lower than 1.9 episodes/child-year in the placebo group [28]. On the other hand, treatment of infants aged 1 to 6 months with diarrhea less than 3 days did not reduce the duration of disease or the number of stools/day in Pakistan, India, Ethopia, or in India [29,30].

ZINC AS REMEDY OF THE COMMON COLD

Rhinoviruses cause 30% to 50% of colds, but scores of other viruses can also be causative agents. Conventional treatment is symptomatic rather than specific for the causative factors. Cold symptoms are likely caused by the release of inflammatory mediators, including selected cytokines and chemokines. The mechanism whereby zinc could act includes a direct antiviral effect, or modulation of the inflammatory response to infection. Nonclinical reports have shown that zinc prevents the formation of rhino viral capsid proteins and the binding of coat proteins to specific receptors on the respiratory epithelium, and it can modulate the amount or function of inflammatory mediators [31,30]. Treatment of patients with common cold has yielded contradictory results. For example, adults and students (mean age, 37 years) in one study with 24 hours or less of cold symptoms who received one(13mg) zinc acetate-containing oral lozenge six times daily had significantly diminished duration of cold symptoms compared with placebo recipients (.4.5 vs 8.1 days; P<.01) [30]. There was no nausea or vomiting, abdominal pain in the zinc group, although gastrointestinal (GI) symptoms and adverse taste of the preparation seemed to unblind some of the zinc trials. Zinc in this study was approximately 80mg/day and zinc level increased from 14.8 to 17.7µmol/Lin contrast, a study of elementary school children who enrolled after 24 hours of cold symptoms and received zinc lozenges,10mg five to six times daily, showed no improvement in cure times (9days) over placebo (9 days) [32]. In a study of subjects 18-65 years of age with colds of 1 day's duration, the median duration of illness was 5.5 days in both the oral zinc acetate group (approximately 70mg/day) and the placebo group [33].

Topical zinc treatment has also been the subject of contradictory reports. On the positive side, within 48 hours of onset of illness, patients received two 12-µ Sprays of a nasal gel containing 33mM of zinc four times daily until symptoms resolved. Their total dose was 960uL. or 2.1mg zinc/day. The duration of symptoms was statistically shortened in the zinc group (4.3 days) compared with the placebo group (6days=.002)[30].

ECHINACEA FOR COMMON COLD

Extracts of the genus Echinacea (purple coneflower) were used by the Native Americans for a wide range of diseases. Including colds, arthritis, snakebite, rabies, seizures, and cancer [34]. Echinacea is hugely popular in Europe and among the top several herbal products in the United States, in terms of annual sales. Echinacea oft-claimed power to prevent or treat upper respiratory tract infections is attributed to the immunologic activity its constituent's manifests in nonclinical models. For example, purified Echinacea polysaccharides activate phagocytes in vitro and in animal models [35]. Despite these claims and in vitro immunologic activities, it has been difficult to prove that Echinacea extracts are truly effective for preventing or treatment of the common colds. In a preventive trial in 40-year old adults who received 4 ml. of fresh expressed juice of whole flowering plants of *Echinacea purpurea* twice daily for 8 weeks, the incidence of natural colds were not statistically reduced (65% in the Echinacea group vs. 74% in the placebo group [35].

Conversely, in another study, adult Germans suffering with incipient cold symptoms who received 5 ml of pressed juice from fresh flowering *E.purpurea*, twice daily for 10 days, demonstrated a statistically significant reduction in median time of illness (6.0 vs. 9.0 days for placebo) [36]. Canadians who received Echinillin (a standardized ehinacea preparation) at the onset of a cold demonstrated statistically significant 23% lowering in total daily symptoms compared with placebo [37].

CHRONIC HEPATITIS AND THE USE OF MILK THISTLE

Milk thistle extract have been used since ancient Rome as treatment for various disorders, including those of liver, and studies have suggested plausible mechanisms whereby they could be beneficial in selected settings. Milk thistle seeds contain approximately 60% silymarin, which is a mixture of six flavanolignan isomers. One isomer, silibinincomprises about half of silymarin. Adminstration of 80 mg silibinin via commercial formulations results in plasma C_{max} values of 200 to 700 ng/ml, and is excreted with a half-life of approximately 6 hours. Bile concentrations of silibinin arte approximately 100 times those found in the serum [38]. Silibinin and other flavonoid are thought to function as antioxidants. Seller and co-workers have reviewed the effects of silymarin and silibinin on cellular metabolism in vitro. Silibinin reacted rapidly with H0 radicals but poorly with 0_2 and H_20_2. Inaddition formation of leukotriene B_2 (but not prostaglandin E_2) was inhibited. In human cells in vitro, silymarin reduced natural cell mediated cytotoxicity but not antigen-dependent cellular cytotoxicity [39]. Clinical evidence, however has suggested that antioxidant or other activities of silymarin may be of only modest benefit in viral hepatitis. In a pilot study of chronic active hepatitis caused by B or C,10 patients who received 240 mgsilibin in twice daily for 7 days demonstrated a statistically significant reduction in hepatocellular enzyme levels. A spartatetransaminase (AST) decreased from 88 to 66 U/Lin silibinin patients, whereas in placebo patients the reduction was 3 U/L [40]. In Egyptians with chronic hepatitis C virus (HCV) infection, the customary dose of Legalon (a milk thistle formulation),140 mg daily for 1 year was no more effective than vitamins in lowering alanine aminotrans ferase (ALT) levels or the percent of patients who were HCV positive [41].

VITAMIN A FOR PNEUMONIA

Vitamin A (retinol) and its metabolites, retinaldehyde and retinoic acid, are needed for vision, growth, cell differentiation, and normal humoral and cell mediated immunity. In children with poor nutrition who present with acute complicated measles, the death rate because of pneumonia may be close to 10% [42]. Vitamin A deficiency in children is associated with increased mortality [43]. It appears that morbidity and mortality from other specific infectious causes is not improved with vitamin A supplementation. Vitamin A prophylaxis of Indonesian children every 4 months for two years, resulted in a rise in acute lower respiratory disease compared with placebo [44]. Vitamin A treatment of Peruvian children with community pneumonia resulted in a modest increase in symptoms [45].

GREEN TEA EXTRACTS FOR HUMAN PAILLOMA VIRUS

External genital warts are associated with human papilloma virus especially types 6 an 11.Topical treatment, for example with 5% imiquimod which activates toll-like receptor 7, increases the 11% placebo cure rate to 50% [46]. Green tea leaves contains 36% polyphenols (catechins) by weight, with epigallocatechingallate (ECgl), and epictechin (EC) comprising, approximately 10%, 5%,5%, and 2% respectively, of dry leaf weight [47]. Polypenon E is an ointment containing 15% green tea polyphenols. Polyphenols are partialy purified; 55% of polyphenon E. phenol is EGCgl, approximately 35% is other phenols, and 2.5% is a combination of gallicacid, caffeine, and theobromine. Polyphenon E have FDA approval for genital warts [48].

HEALTH BENEFIT AND THE RISKS OF PROBIOTIC USE

The mechanism of clinical benefit is postulated to be via GI immune mechanism. Colonization bacteria interact with cells, including immune cells of the gut epithelium, and probiotic bacteria could enhance mechanisms such as natural killer cell activity [49]. Probiotics might also be effective by a simple nonimmunologic mechanism, preventing pathogen adherence and invasion of gut tissues [49]. Recent finding suggest that probiotics may help in atopic eczema, irritable bowel syndrome, and inflammatory bowel disease and *Helicobacter pylori* infections [50]. Probiotics have been used for acute diarrhea, allergies, colitis, inflammatory bowel disease and irritable bowel syndrome, the strongest evidence for efficacy is in the treatment and prevention of acute diarrhea [51]. In a recent randomized, double blind placebo-controlled trial designed to evaluate the effectiveness of probiotic preparation, (6 different Lactobacillus or *Biofidobacterium*, Strains; total daily dose 10^{10}bacteria) on infectious complications of acute pancreatitis reported increased mortality in probiotic treatment group (16% in 152 patients treated with probiotics vs. 6% in 144 patients treated with placebo, relative risk 2.53,95% confidence intervals 1.22-5.25) without any measureable impact on infectious complications [50].

PRECAUTION IN THE USE OF CAM

Medicinal plants are effective against such bacterial pathogens (e.g. *Streptococcu*s, and *Pseudomonasaeruginosa*) Their medicinal use in infections associated with these two species is not recommended [52]. Patients should use caution when combining garlic supplements with saquinavir (For tovase) when it is used as a sole protease inhibitor [53]. The public is often unaware that CAMs are not tested by the Therapeutic Goods Administration for efficacy and safety [54].

CONCLUSIONS

Complementary and alternative medicines (ACM) are widespread use, for their health benefits. Their use in certain clinical conditions must be with caution and CAM is not tested for safety and efficacy.

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